REMARKS

Applicants thank the Examiner for consideration of the subject patent application. In the Advisory Action mailed January 31, 2008, Claims 81-84, 86, 98, 100, and 102-103 were pending. The applicants have canceled now claims 98 and 100. Additionally, the Applicants have amended Claim 81. As such, Claims 81-84, 86 and 102-103 remain pending.

CLAIMS

Applicants have currently amended Claim 81 to recite a permeation enhancer of fatty acid esters of lactic acid. It is noted that the present amendment is within the scope of the originally elected species of fatty acid esters as filed in the Applicants response dated June 18, 2007. The present narrowing amendment of the permeation enhancer species is intended to facilitate and accelerate the allowance of the pending claims. Support for the amendment can be found in original Claim 81 as well as page 23, lines 13-17; and page 24, lines 21-22. Additionally, Claim 81 has been amended to clarify the rubber-based pressure sensitive adhesive as including copolymers as found on page 36, line 9. Claims 98 and 100 have been canceled. As such, no new matter has been added.

Further, inasmuch as a permeation enhancer of fatty acid esters of lactic acid was previously recited as part of Claim 81, and is included within the species previously elected, the present amendment does not include any new matter outside the scope of previous Claim 81 which raises new issues or would require a new search.

35 U.S.C. § 112, first paragraph

Applicants have amended Claim 81 to clarify that the acrylate polymer includes homopolymers, copolymers, and terpolymers thereof as found on page 33, lines 20-21 of the specification and that the rubber-based pressure sensitive adhesive includes copolymers as found on page 36, line 9 of the specification. Additionally, Applicants have canceled claims 98 and 100 which recite lauryl lactate. As such, Applicants submit that the pending claim set only contains material that is supported from the application and respectfully requests that the Examiner withdraw the present rejection.

35 U.S.C. § 103

The Examiner has rejected Claims 81-84, 86, 98, 100, and 102-103 under 35 U.S.C. 103(a) as allegedly being unpatentable over U.S. Patent No. 6,352,715 (hereinafter "'715"), Chinese Patent No. 1111987 (hereinafter "'987") and U.S. Patent No. 6,262,063 (hereinafter "'063").

The Applicant does not deem it necessary to recite the entire case law standard required in order to establish a *prima facie* case of obviousness. However, the Applicant would like to briefly remind the Examiner of the required three criteria for a *prima facie* case of obviousness, namely 1) that the asserted references as modified or combined must teach or suggest each and every element of the claimed invention, 2) that the asserted references as modified or combined must provide a sufficient likelihood of successfully making the modification or combination, and 3) that the Examiner must identify a reason for the modification or combination asserted. Nothing in the recent *KSR* Supreme Court case changes this basic analysis.

Specifically, the Examiner has rejected Claims 81-84, 86, 98, 100, and 102-103 as being obvious in view of two combinations: '715 in view of '063 and '987 in view of '063. As such a brief description of these references is provided below.

The '715 Reference

The '715 reference relates to a transdermal delivery system for Huperzine A. See Abstract. Generally, the '715 reference focuses on pH as a means to increase permeation of the drug and concludes that the only form of huperzine able to penetrate the skin is the neutral form. See col. 2, lines 65-67. The '715 reference further speculates that a possible method to further improve delivery of the neutral form of huperzine is to increase concentration of undissociated huperzine at the huperzine source, by adding non-polar solvents such as alcohols and glycols. See col. 8, lines 41-49. Such speculation also comes with the strong caution that, "However, these agents also reduce partitioning of drugs across the skin. Thus, various co-solvents need to be evaluated so as to achieve balance of satisfactory solubility and partitioning." See col. 8, lines 49-53.

The '987 Reference

As noted by the Examiner, the '987 reference is directed at a plaster containing Huperzine. See Abstract. Specifically, '987 mandates Azone (laurocapram) as a permeation enhancer either alone or in combination with another permeation enhancer. Azone is always taught as a required permeation enhancer. As noted by the Examiner, '987 does not teach the permeation enhancer presently claimed.

The '063 Reference

The '063 reference is directed at the treatment of tinnitus using a variety of agent classes included muscarinic and/or opiod agents, preferably an anticholinesterase inhibitor, such as neoostigmine. See Abstract. An extensive list of varying active agents is set forth on beginning in Col. 2, line 60 and running through Col. 3, lines 65. The compositions are generally delivered as ear drops to the ear canal. See Examples. The '063 reference discloses numerous types of agent that may be used including 12 acetylcholinesterase inhibitors, one of which is Huperzine. See col. 2, lines 60-67 and col. 3, lines 1-4. The compositions can be administered in various regimes but are disclosed as being administered at least daily. See col. 4, lines 38-45. The '063 reference also discloses an extensive laundry list of penetration enhancers including Azone and lauryl lactate. See col. 5, line 36 – col. 4, line 11. There is no teaching or correlation of any of the numerous active agents or active agent classes with any of the specific permeation enhancers.

The Examiner has argued that the present invention is obvious in view of either of the two primary references ('715 or '987) in view of the same secondary reference ('063). Each of the combinations of references are discussed in detail below, beginning with the combination of the '715 reference with the '063 reference. The Examiner has stated that the '715 does not teach the presently claimed permeation enhancers.

The Examiner has alleged that the '715 reference suggests the use of co-solvents as a means to enhancer permeation. Although the '715 reference briefly mentions that co-solvents may used to "increase the concentration of undissociated form of Hup A," there is no teaching that such solvents

can be used as permeation enhancers. The teaching regarding the co-solvents is merely to increase the concentration of "undissociated" Hup A, which is taught by the reference to be more readily delivered. In fact, the '715 actually teaches away from the idea that the co-solvents are used as "permeation enhancers." Specifically, the '715 reference explicitly states that "these agents [co-solvents] also reduce partitioning [i.e. permeation]of drugs into the skin." (emphasis added) Further warning that each co-solvent needs to be "evaluated" so that it does not adversely effect permeation of the Hup A. In short, the '715 reference not only fails to teach the use of co-solvents **as permeation enhancers**, the reference actually warns against the indiscriminant use of such co-solvents as they can negatively effect permeation of the drug into the skin. As such, '715 teaches away from the present combination asserted by the Examiner.

As the Applicant has raised the issue of teaching away, the Applicant would like to review the current case law regarding teaching away for the Examiner's convenience. The Court of Appeals for the Federal Circuit has clearly stated that "an applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect." In re Petersen, 315 F.3d 1325, 1331 (Fed. Cir. 2003). The Court has also stated that "[w]e have noted elsewhere, as a 'useful general rule,' that references that teach away cannot serve to create a prima facie case of obviousness." (emphasis added) McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1354 (Fed. Cir. 2001). In identifying the appropriate standard for teaching away, the Court has further stated:

> "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be **discouraged from following the path set out in the reference**, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular

> facts; in general, **a reference will teach away if it suggests** that the **line of development** flowing from the reference's disclosure **is unlikely to be productive** of the result sought by the applicant." (emphasis added) In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Clearly in the present case, a person of ordinary skill in the art is disincentivised from attempting to use an co-solvents to enhance permeation as this is not the expressed reason for their use in the '715 reference to begin with. Rather it is to increase concentration of the non-polar form of huperzine at the huperzine source. Assuming *arguendo* that there were some suggestion to utilize cosolvents to enhance penetration, one of ordinary skill in the art would be very discouraged from deviating from those agents mentioned and interchanging co-solvents, including those of the '715 composition with any of the compounds present in the extensive list of permeation enhancers set forth in the '063 reference in view of the strong warnings given by the '715 reference. As discussed above, there is no teaching or correlation in the '063 reference regarding which permeation enhancers are effective with which active agents. Based on this, any combination of the teachings of the '063 reference and the '715 reference would require undue experimentation in order to determine which, if any, of the permeation enhancers listed might work.

As discussed with the Examiner in the most recently held interview, formulating transdermal delivery formulation, in this case a transdermal matrix patch, is a very complicated and process with many variables and a high amount of unpredictability. Specifically, effective penetration enhancers for specific active agents are not easy to identify. The Applicants submit that such teachings regarding the fickle and unpredictable nature of penetration enhancers are

generally known in the art. Examples of third party teachings of such a concept can be found in U.S. Patent No. 5,500,222 which also describes permeation enhancers in the same fashion:

> No "universal" permeation enhancer has been identified. Instead, the behavior of permeation enhancers is highly idiosyncratic; a permeation enhancer effective for one drug may not be effective with other drugs, including closely related drugs.
>
> Often, a permeation enhancer will exacerbate irritation and sensitization problems by allowing high transdermal permeation rates of the drug or permeation enhancer or permitting otherwise impermeable components of the transdermal device to enter the skin. Many potential permeation enhancers interact adversely with other components of transdermal devices. One major problem is that many potential permeation enhancers are not compatible with medically acceptable contact adhesives. Enhancers may improve the transdermal permeation rate adequately, but not adequately reduce the lag time.
>
> The use of a permeation enhancer in any transdermal drug delivery device necessarily complicates the design and development of the device. Permeation enhancers cause compatibility problems throughout the delivery system. Instead of having to characterize the properties of the reservoir compositions, adhesives, and release-controlling materials with respect to just the drug, these materials must now have the proper characteristics with respect to both the drug and the permeation enhancer. Typically, drugs and permeation enhancers have very different physical and chemical properties, and, in most cases, the properties of mixtures of the drug with the permeation enhancer are unknown. For example, permeation enhancers can cause, among other problems, cohesive failure of adhesives and can partition through other components in the system. See col. 2, line 47 through col. 3, line 12.

Based on the above teachings regarding the difficulty of formulating transdermal systems and identifying permeation enhancers which can be functional in the transdermal systems, Applicants submit that indiscriminately combining a transdermal system with a permeation enhancer contrary to the knowledge of one of ordinary skill in the art, and in fact, such a practice would not be expected to provide any likelihood of success based on the knowledge of permeation enhancer behavior currently known in the art. As such, Applicants submit that, based on the teachings of the '715 reference

regarding the detrimental effects of some co-solvents on drug penetration, one skilled in the art would not combine the teachings of the '715 reference and the '063 reference in order to arrive at the presently claimed invention, absent impermissible hindsight reconstruction, particularly in light of the fact that the '063 reference makes no correlation between any specific active agent and any specific permeation enhancer, let alone huperzine and lauryl lactate.

Additionally, Applicants note that the Examiner is attempting to combine one possible permeation enhancer from a laundry list of permeation enhancers with one specific active agent (i.e. huperzine) even though there is no motivation to choose any specific enhancer. In other words, Applicants submit that the one of ordinary skill in the art, upon reviewing the present combination of references, would have no reason to specifically select a fatty acid ester of lactic acid (i.e. lauryl lactate) out of the laundry list of enhancers taught in the '063 reference and combine it with the transdermal system of the '715 reference. Therefore, Applicants contend that any such combination would necessarily be based on impermissible hindsight.

As the Applicant has raised the issue of hindsight analysis, the Applicant would like to review the current case law regarding hindsight analysis for the Examiner's convenience. The court has stated that the Applicant's specification cannot be the basis for motivation, i.e., no hindsight reconstruction. Yamonouchi Pharmaceutical Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 56 U.S.P.Q.2d 1641(Fed. Cir.), reh'g denied, 2000 U.S. App. LEXIS 34047 (2000). Accordingly, if a prior art reference is sought to provide a specific element of a claim with the use of hindsight, any rejection based thereon is improper and should be withdrawn.

The Applicants submit that the present combination fails to teach each and every element of

the present claim set, that there is no likelihood of success in making the present combination, and that there is no reason to make the specific combination based on the knowledge available in the art. As such, the Applicants submit that the Examiner has not made a *prima facie* case of obviousness and respectfully request that the Examiner withdraw the present rejection.

The Examiner has also combined the '987 reference with the '063 reference in rejecting the pending claim set. However, such a combination does not provide a likelihood of success and does not teach each and every element. Additionally, there is no apparent reason to make such a combination based on knowledge available in the art.

The Applicants renew the above arguments with respect to this combination. Specifically, based on the knowledge of permeation enhancer behavior (see above and U.S. Pat. No. 5,500,222), combining a permeation enhancer from a laundry list with a specific transdermal system would have no likelihood of success. Additionally, such a combination would be necessarily from hindsight as neither reference (nor knowledge available from the art) could direct one skilled in the art, to specifically choose a fatty acid ester or lactic acid and combine it with the transdermal system of the '987 reference.

Additionally, the Applicants submit that, even if one skilled in the art would combine the '987 reference with the '063 reference, such a combination would require the use of Azone as a permeation enhancer since '987 explicitly mandates the use of Azone, alone or in a combination or mixture with another penetration enhancer as agreed to during the interview. The currently pending claims specifically exclude the use of Azone due to Azones inability to provide the claimed delivery profile. As such, in order to derive the present invention from the '987 reference, alone or in

combination with any other reference, one would need to destroy the teachings of the '987 reference, namely the inclusion of Azone as a permeation enhancer. As such, the '987 reference, alone or in combination with any reference, cannot render the presently pending claim set obvious.

The Applicants submit that the present combination fails to teach each and every element of the present claim set, that there is no likelihood of success in making the present combination, that there is no reason to make the specific combination based on the knowledge available in the art, and that the combination effectively destroys the teachings of the '987 reference. As such, the Applicants submit that the Examiner has not made a *prima facie* case of obviousness and respectfully request that the Examiner withdraw the present rejection.

Response to Arguments

The Examiner has alleged that the '715 reference and the '987 reference suggest permeation enhancers and that the '063 reference teaches the equivalency between fatty acids and their esters and azone in terms of skin enhancing effect, and this teaching would have motivated one skilled in the art to include fatty acid esters in the transdermal delivery systems disclosed in '715 and '987. However, such a statement is misleading. The '063 reference does not teach any equivalency between the listed permeation enhancers, only that such compounds are generally known as permeation enhancers. However, as previously discussed, such knowledge is insufficient to establish that a specific enhancer is compatible with s specific system. As outlined in the '715 patent and further support in the art (also supported by the 5,500,222 patent), there is no universal permeation enhancer and that such enhancers cannot be indiscriminately combined or exchanged. Additionally, the Applicants submit

that there is absolutely no reason one skilled in the art, upon reading the present references, would specifically select a fatty acid ester of lactic acid and combine such an enhancer with the transdermal systems of the '715 reference or the '987 reference. Furthermore, the Applicants submit that the explicit teaching of the '715 patent and knowledge available in the art would teach away from making such a combination. Also, Applicants submit that the '987 combination with '063 would result in a transdermal system that necessarily contains Azone which has been explicitly excluded from the present claims.

CONCLUSION

If any impediment remains to further examination of the present application after consideration of the above-recited election and remarks, which could be removed during a telephone interview, the Examiner is invited to telephone the undersigned attorney at (801) 566-6633 so that such issues may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. 20-0100.

DATED this 15th day of February, 2008.

Respectfully submitted,

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